HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

James Conover, Ph.D.
Executive Director
U.S. Regulatory Affairs
Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

FEB 22726 '00 MAR -6 A9:45

Re. Docket No. 78N-036L
Comment No. RPT 13

Dear Dr. Conover:

Reference is made to your submission dated June 30, 1999, identified as Comment No. RPT 13, under Docket No. 78N-036L in the Dockets Management Branch, in which your company submitted the results of analytical and toxicity testing conducted by various companies on senna and a protocol for a proposed industry-wide 2-year rat carcinogenicity study of senna. In addition, you submitted a rationale for conducting a single 2-year carcinogenicity study using powdered senna pods to evaluate the potential carcinogenic activity of all marketed senna and sennosides products. You submitted this information to support the safety of senna as a Category I (safe and effective) over-the-counter (OTC) laxative drug ingredient.

Your submission contained 14-day and 13-week oral dose range finding studies in which rats received either powdered senna pods (purity stated as 5 percent) or sennosides (purity stated as 96.3 percent). You proposed doses of 25, 200, and 600 mg/kg/day for a 2-year carcinogenicity study with powdered senna pods in Sprague-Dawley rats based upon the results of the 13-week oral dose range finding study. You indicated that the powdered senna pods batch(es) for use in the proposed study contain all compounds (i.e., all components of pharmacological and toxicological relevance) found in all marketed senna products.

We have reviewed your submission and other information available on senna. We have the following recommendations and conclusions regarding your proposed 2-year rat carcinogenicity study. This information was discussed in the minutes of the September 29, 1999 Pharmacology/Toxicology Senior Policy Team/Special Executive Carcinogenicity Assessment Committee Meeting, which we provided to you on October 30, 1999.

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1. It is acceptable to use powdered senna pods (to be supplied by Madaus AG) in the 2-year study. Natural senna (i.e., powdered senna pods), used in most laxative products, contains a complex profile of compounds. The sennoside extract, used in some laxative products, contains a smaller number of the compounds found in powdered senna pods. Based on your quantitative measurements of different types of senna products, the powdered senna pods preparation proposed for use in your 2-year rat carcinogenicity study appears to contain the complete profile of compounds found in natural senna and sennoside extract products. The results of the 2-year rat carcinogenicity study will be considered generally representative of marketed senna drug products.

2. The observed toxic effects in 13-week oral dose range finding studies with powdered senna pods and sennoside extract appeared identical based upon histopathology findings of renal lesions and mucosal hyperplasia in the cecum, colon, and rectum. The differences in doses between the two products is probably related to concentrations of the active moieties.

3. The study protocol for the 2-year carcinogenicity study appears acceptable provided the doses are changed (see item 4 below). Histopathological analysis of major organs and tissues in all animals and drug administration by oral gavage is acceptable. You should also perform a full histopathological analysis on all animals that die or are sacrificed in a moribund condition during the treatment period.

4. Revise the doses to 300, 100, and 25 mg/kg/day. We recommend these doses because renal lesions were observed at doses ≥ 300 mg/kg/day in the dose range finding study.

5. The definition and basis of "purity" of the powdered senna pods in the 13-week dose range finding study as well as the 2-year rat carcinogenicity study should be provided. The definition and basis of "purity" of the sennoside extract in the 13-week dose range finding study should also be provided.

6. The sponsor should consider obtaining pharmacokinetic data from human subjects following oral administration of senna for comparison with toxicokinetic data obtained from rats to

facilitate interpretation of any tumor findings.

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1061, 5630 Fishers Lane, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

Charles Ganley, M.D.

Charles Ganley, M.D.
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research